Diabetes and cognitive impairment: how to evaluate the cognitive status?

F. Pasquier

Université Lille-Nord-de-France, UDSL, EA 1046, CHRU, Hôpital Roger Salengro, 59037 Lille cedex, France

Abstract

Aim. – Patients with diabetes have shown lower performance in tests of cognitive function especially those testing memory, executive functions, and psychomotor efficiency. They also have an elevated risk of both vascular dementia and Alzheimer’s disease. Cognitive impairment may have consequence on treatment compliance.

Methods and results. – This article provides indication for holding an interview, and reports a few screening bedside tests to detect a cognitive impairment. Some neuropsychological tests useful for characterizing the cognitive profile of a patient are described, as well as the main cognitive profiles expected in patients with diabetes and cognitive decline.

Conclusion. – A systematic assessment of cognition with a rapid interview and screening tests in patients with diabetes, especially the oldest, with a long history of diabetes, co-morbidities, or with unexplained poor metabolic control would be a good clinical practice. Patients with cognitive decline may be referred to memory clinics for identifying the cause of the decline and contribute to provide appropriate medical and medicosocial management.

Keywords: Diabetes; Cognition; Neuropsychology; Dementia; Review

Résumé

Diabète et altérations des fonctions cognitives : comment évaluer le statut cognitif ?

Objectif. – Il a été montré que les patients diabétiques avaient des performances moins bonnes que les sujets non diabétiques notamment sur les épreuves testant la mémoire, les fonctions exécutives et qu’ils présentaient un ralentissement psychomoteur. Les patients diabétiques sont aussi à risque plus élevé de démence vasculaire et de maladie d’Alzheimer. Or les troubles cognitifs pourraient avoir des conséquences sur l’observance thérapeutique.

Méthode et résultats. – Cet article donne des indications sur la manière d’interroger un patient en vue de repérer un déclin cognitif, et décrit quelques tests de dépistage d’un déclin cognitif réalisables en consultation ou au lit du malade. Il décrit également quelques tests neuropsychologiques (réalisés généralement par des psychologues) utiles pour caractériser le profil cognitif d’un patient et les principaux profils cognitifs attendus chez un patient diabétique.

Conclusion. – L’évaluation systématique de la cognition par quelques questions pertinentes et des tests de débrouillage est de bonne pratique chez les patients diabétiques notamment les plus âgés, ayant une longue histoire de diabète, présentant des co-morbidités, ou un mauvais contrôle métabolique avec des complications. Les patients chez qui des troubles cognitifs sont suspects peuvent être adressés à une consultation mémoire pour la recherche de la cause de ce déclin et contribuer à la prise en charge thérapeutique et médico-sociale la plus appropriée.

Mots clés : Diabète ; Cognition ; Démence ; Neuropsychologie ; Revue générale

1. Introduction

The impact of diabetes on cognitive function, especially memory, psychomotor efficiency, and executive function, is addressed for a long time [1]. Compared to people without diabetes, people with diabetes have a greater risk of cognitive decline [2], especially memory and executive functions [3, 4]. There is also evidence for an elevated risk of both vascular dementia and AD in patients with type 2 DM albeit with strong interaction of other factors such as hypertension, dyslipidaemia and apolipoprotein E genotype [1].

Some tests that have shown lower performances in not demented patients with diabetes than in controls [5–7] including the Digit Symbol Substitution Test (DSS) from the
functions, orientation and language. Some scales like the one necessary to detect and orient towards a cognitive decline.

Results are inconsistent, and other factors are involved in cognitive impairment of patients with diabetes, including age, co-morbidities, level of education, duration, and control of the disease. However, it remains a good clinical practice to systematically assess cognition in older patients with a long history of diabetes or with co-morbidities, as well as patients with poor control of their glycaemia and in patients having complications of DM.

2. Why assessing cognition?

Assessing cognition has several aims. It may indicate whether the patients need supervision for managing their treatment, and improving metabolic control leads to better cognitive functions in patients with Type2 diabetes [12]. Executive functions are involved in organization of information, carrying out plans, judgment according to outcome and cognitive shifting. They are regulated by the dorsolateral prefrontal cortex (PFC), whereas ventral PFC regulates decision making [13] by predicting future rewards and punishments and inhibits impulsive thoughts and responses. Insulin is an important central signal to regulate PFC functions, attenuated in diabetes [14]. In addition to impairment in memory and judgment which have consequence to treatment compliance, impairment in PFC function is particularly important in patients with type 2 diabetes, who are required to make strict daily decisions for optimal glycemic control [15].

Characterising the profile of cognitive impairment helps to diagnose the underlying pathology, more or less related to diabetes. Diabetes is a vascular risk factor and cerebrovascular lesions may cause cognitive impairment. Patients with diabetes may suffer, as others, from degenerative diseases such as Alzheimer’s disease (AD) and other degenerative disorders namely Lewy body disease or frontotemporal lobar degeneration. Furthermore, there is some evidence that patients with diabetes may be at risk for AD. The mechanisms underpinning this association remain to be clarified. It is likely that multiple different, synergistic processes may interact to promote cognitive decline [16].

3. How to assess cognition in clinical practice?

3.1. Interview

First an interview with the patient and an informant is necessary to detect and orient towards a cognitive decline. Questions should be first about episodic memory and executive functions, orientation and language. Some scales like the one of McNair et al. [17], previously an auto-questionnaire, or the “Questionnaire de Plainte Cognitive (QPC)” [18] help to structure the interview. For example, the following questions could be asked:

3.1.1. Concerning memory

Did you notice any change in your memory functioning compared to what it was 6 months ago? Do you think your memory is functioning as well as that of other people of your age? In the last 6 months did you feel that registration of new memories is worse than previously? In the last 6 months, did you forget more appointments than you used to forget before? Did you loose your belongings more often than previously? Did you ever completely forget an event even after your relatives told it to you or showed you pictures related to it?

3.1.2. Concerning executive functions

Did you give up some activities or asked for being helped in some activities because of fear to make mistakes or because you are less self-confident than before? Do people find you less interested in some of your previous activities or that you have less initiative than before? Do you feel having more difficulties to do things that you performed quite easily before, because you do not know how to start and to plan each step to achieve them (e.g. organising a trip, inviting people to eat, or sending tax return...).

3.1.3. Concerning language

Do you have the feeling that you miss some words, so that you need to replace these words, use words like “thing”, or locution like “what do you call it?” more often than usual? Do you have difficulties with comprehension? Do you sometimes misunderstand what is said or written?

3.1.4. Concerning orientation

Do you have more difficulties in orientation in space, notably in unfamiliar places?

As for any complaint, it must be asked for how long the patient noticed the change; if this change is noticed also by the relatives or by colleagues; if it happened suddenly, in a subacute fashion, or insidiously; and if the progression is stable, improves or worsens.

It is also important to know whether this cognitive change is associated with other symptoms, especially mood or behaviour changes, and if the neurological examination has changed (e.g. appearance of new focal symptoms).

3.2. Global assessment

The multi-item rating scales and batteries of brief cognitive tests evaluate several cognitive functions. Scores on various
separate items or tests are summed to provide a total score representing overall cognitive status. The sensitivity of these cognitive tests in short formats is not uniform and varies by age, education, social class and living situation (e.g. at home, independent of family members, in a geriatric institution, in hospital) [19]. However, they are useful in assessing the rate of cognitive decline, and grading the severity of dementia.

- **The mini-mental status examination (MMSE)** [10] is one of the most widely used screening tests of cognitive decline. The MMSE scale ranges from 0 to 30 points, with higher number indicating better performance. The MMSE consists in questions designed to assess the patient’s mental status in the following 7 categories:
  - Orientation in time (5 points): year, season, date, day, month
  - Orientation in space (5 points): country, city, street (or building), floor and location
  - Short term memory (3 points): repetition of 3 words (concrete and frequent words); the patients are informed that they have to learn these words, which have to be recalled later.
  - Counting backwards (5 points): subtraction of seven serially (100-7; 93-7; 86-7; 79-7; 73-7; 65) which is also a distraction task between learning and recall of the 3 words (to prevent repeating the 3 words mentally)
  - Episodic memory (3 points): delayed recall of the 3 previously repeated words
  - Language (8 points): confrontation naming of 2 items (watch and pencil, 2 points), repetition of the sequence “No ifs, ands, or buts” (adapted to French language as “pas de mais, de si, ni de et” http://cat.inist.fr/?aM odel=e=afficheN&cpsidt=15201642, 1 point); writing a sentence (1 point), oral comprehension of a 3 step-command (take the sheet of paper, fold it in 2 and put it on the floor, 3 points), read and follow the sentence “close your eyes” (1 point)
  - Constructional praxis: copy of overlapping pentagons (1 point).

The performance in the MMSE can be influenced by age and education level. Usually the cut-off to consider a possible dementia is 26 for patients with more than 8 years of education (and 18 in patients with 1 to 8 years of study). MMSE has disadvantages for the screening of vascular cognitive impairment: it emphasizes language and verbal memory, it lacks the recognition part of memory, it has no timed elements, and it is not sensitive to impairments in executive functions or mental slowing. A low MMSE score was shown to be significantly associated with reduced activities of daily living, increased need for assistance in personal care, and higher hospitalisation rates [20].

An other more an more widely used test it the Montreal Cognitive Assessment (MoCA, http://www.mocatest.org/) which is a cognitive screening test designed to assist for detection of mild cognitive impairment. It assesses different cognitive domains: attention and concentration, executive functions, memory, language, visuo-constructional skills, conceptual thinking, calculations, and orientation. Time to administer the MoCA is approximately 10 minutes. The total possible score is 30 points; a score of 26 or above is considered normal. It was shown to be superior to the MMS for the detection of vascular cognitive impairment since it detects more cognitive abnormalities, particularly in executive function, attention and delayed recall [21]. It is more capable of testing for complex cognitive impairments in domains such as visuo-spatial, executive function and abstract reasoning than the MMSE. In addition, the MMSE subtests of Attention and Delayed Recall contain test items which are not as challenging as contained in the MoCA. For example, the only MMSE test for attention is the serial 7s test while the MoCA includes 2 additional tests: Digit Span (forward , 5 numbers, and backward, 3 numbers) and Vigilance (The examiner reads the list of letters at a rate of one per second, after giving the following instruction: “I am going to read a sequence of letters. Every time I say the letter A, tap your hand once. If I say a different letter, do not tap your hand”). Similarly, the 3-item Delayed Recall in the MMSE is less difficult than 5-item Delayed Recall in the MoCA, which also includes a brief executive function assessment (the trail-making test, and a verbal fluency test), and an abstraction test (Tell me how an orange and a banana are alike).

4. Neuropsychological tools

4.1. Bedside tools

A selection of common widely used tools sensitive to cognitive decline is presented.

4.1.1. 5 Words Test [22]

It is a serial verbal episodic memory test, with semantic cueing. Five words of 5 different semantic categories (grass-hopper, lemonade, museum, colander, lorry) are presented to the patients who are asked to read aloud and learn these words. Encoding is controlled by asking the patients to tell what is the building, the vehicle, the drink, the insect, the cookware when looking at the list of words. Then the list of words is removed, and the patients are asked to recall the 5 words (immediate recall). If one or more words are missing, the examiner provides the cue (e.g. there was a fruit, do your remember it?). If the word is not found, the examiner reminds it to the patients. After a delay, and an interfering task, recalling the words is asked again (delayed free recall), and a cue is provided as well to help recalling the missing words if any (delayed cued recall). The total score is 10 (five for the immediate recall, sum of the free and cued recall, and five for the delayed recall as well). The cut-off for this test is 10 (since it is not very sensitive, but highly specific).

Normal aged subjects displayed good encoding, efficient storage, and consolidation (few forgetting, efficient cued recall),
and intrusions are rare. Patients with the amnestic hippocampal syndrome (like in mild Alzheimer’s disease) are characterized by weak encoding of words and severe deficit for storage and consolidation (important forgetting, impaired cued recall), and they make numerous intrusions. On the opposite, subcortical, and frontal dysfunction, like in vascular cognitive impairment, is characterised by low free recall scores, efficient cueing (although less efficient than in controls) and no forgetting between immediate and delayed total recall (i.e. free + cued recall). Recognition id better than recall, and provision of multiple-choice alternatives enhances performance.

4.1.2. Isaacs set test [23]

The Isaacs Set Test shortened at 15 seconds evaluates verbal fluency abilities and speed of verbal production. Subjects have to give a list of words (with a maximum of 10) belonging to a specific semantic category in 15 seconds. Four semantic categories were successively used (cities, fruits, animals, and colours). The score ranges from 0 to 40. It is a good test to measure cognitive changes, since it does not suffer from a floor effect of a ceiling effect.

4.1.3. Frontal Assessment Battery (FAB) [24]

It is a short cognitive and behavioural battery to assess frontal lobe functions. It consists of 6 subtests exploring: 1) conceptualization (similarities: in what way are they alike? Table and chair, tulip rose and daisy); 2) mental flexibility (lexical fluency: say as many words as you can beginning with the letter “S”); 3) motor programming (learning of a gestural sequence, series of Luria: fist-edge-palm); 4) sensitivity to interference (conflicting instructions: tap twice when I tap once); 5) inhibitory control (Go-No-Go: tap once when I tap once; do not tap when I tap twice); and 6) environmental autonomy (prehension behaviour: do not take my hands). It takes approximately 10 minutes to administer. It correlates with other frontal lobe tests. Frontal lobe functions may be especially impaired in vascular subcortical lesions.

4.1.4. Clock Drawing Test [25]

The patient is asked to draw a clock put in all the numbers, and set the hands at ten past eleven. This test provides information about general cognitive functioning, visuo-spatial abilities and constructional praxis.

4.2. Neuropsychological tools

To further explore a cognitive decline, a few commonly used tests are presented, generally administrated by neuropsychologists, in a standardized way. Each neuropsychologist is accustomed to using his/her own battery. The most important thing in clinical practice is to use pertinent tools to detect and characterize a dysfunction.

4.2.1. Mattis dementia rating scale (DRS) [26]

It was designed as a screening instrument to detect the presence of brain pathology in impaired geriatric patients. It evaluates a broad array of cognitive functions and includes subtests for attention, initiation-perseveration, construction, conceptualization, verbal and nonverbal memory. Its administration requires 15-30 minutes. It is sensitive to frontal and fronto-subcortical dysfunctions. It is useful in the assessment and progression of dementia including Alzheimer’s disease, subcortical dementias such as vascular dementia, Parkinson’s disease, and Huntington’s disease, and age-related dementia in mental retardation and Down’s syndrome.

4.2.2. Free and cued selective reminding test [27]

This test has inspired the 5 words test. But in this long version of the test, there are 16 words to be remembered, presented 4 at a time on a card. There are 4 phases: 1) Encoding and immediate cued recall; 2) Free and cued recall (3 series); 3) Yes-no recognition of the 16 to-be-remembered words among 16 semantic and 16 neutral distractors. 4) Free and cued delayed recall, 20 minutes after the recognition test.

4.2.3. Frontal lobe test

- The Wisconsin Card Sorting test (WCST) measures executive function closely related to the dorsolateral prefrontal cortex. Four stimulus cards and one response card are shown; the cards had geometric designs divided into three categories: colour, form and number of sets. The subjects are asked to decide how to categorise a response card to the four cards, and to search for the correct categorisation by trial-and-error. The achievement scores are related to working memory. Perseverative errors are related to cognitive shifting ability, as the errors are caused by adhering to a former category after the classification category had changed.
- The Stroop test: subjects are tested on naming colours of incompatible words and of control patches (after reading words in black). The interference score is expressed as the difference between the times needed to read each of the two types of cards [28].
- The Trail Making test (part A and B) assesses the mental flexibility. Both parts of the Trail Making Test consist of 25 circles distributed over a sheet of paper. In Part A, the circles are numbered 1 – 25, and the patient should draw lines to connect the numbers in ascending order. In Part B, the circles include both numbers (1 – 13) and
letters (A – L); as in Part A, the patient draws lines to connect the circles in an ascending pattern, but with the added task of alternating between the numbers and letters (i.e., 1-A-2-B-3-C, etc.). The patient should be instructed to connect the circles as quickly as possible, without lifting the pen or pencil from the paper.

- Tests of social cognition and theory of mind. Theory of mind is the ability to attribute mental states – beliefs, intents, desires, pretending, knowledge, etc.—to oneself and others and to understand that others have beliefs, desires and intentions that are different from one’s own. Test of social cognition may help to explain behavioural changes related to frontotemporal dysfunction: decision-making, recognition of facial emotion and cognition, “faux pas”, false belief, etc.

5. Other assessment tools

5.1. Functional scales

- Instrumental Activities of Daily Living (IADL) [29] designate the activities often performed by a person who is living independently in a community setting during the course of a normal day, such as managing money, shopping, telephone use, travel in community, housekeeping, preparing meals, and taking medications correctly. Four activities are particularly sensitive to cognitive impairment, and thus a change in them must be especially searched for: 1) Ability to use telephone (from “operates telephone on own initiative, looks up and dials numbers etc” to “does not telephone at all”, with intermediate levels of loss of autonomy: “dials a few well-known numbers” and “answers telephone but does not dial”); 2) Mode of transportation (from “travels independently on public transportation or drives own car” to “does not travel at all” with intermediate levels “arranges own travel by taxi, but does not otherwise use public transportation”, “travels on public transportation when accompanied by another”, and “travels limited to taxi or automobile with assistance of another”); 3) Responsibility for own medication (from “is responsible for taking medication in correct dosages at correct time” to “is not capable of dispensing own medication” with an intermediate level; “takes responsibility if medication is prepared in advance in separate dosage”); 4) Ability to handle finances (from “manages financial matters independently”, i.e. budgets, writes checks, pays rent, bills, goes to bank to “incapable of handling money” with an intermediate level “manages day-to-day purchases but needs help with banking, major purchases etc”). Any change from a higher level of independency, not due to physical problems, is highly suspect of cognitive decline. Loss of autonomy is part of the definition of dementia.

- Much comprehensive scales such as the Alzheimer’s Disease Cooperative Study Activities of Daily Living (ADCS-ADL) [30] may also be used.

5.2. Behavioural scales

- The Neuropsychiatric Inventory Questionnaire (NPI-Q) is a rapidly administered instrument that provides a reliable assessment of mood and behaviours commonly observed in patients with cognitive impairment or dementia. It assesses the severity of the symptom in the patient and the distress the symptom causes in the caregiver [31]. It questions about delusions, hallucinations, agitation or aggression, depression or dysphoria, anxiety, elation or euphoria, apathy or indifference, disinhibition, irritability or lability, motor disturbance (i.e. repetitive activities, or restlessness), night-time behaviours and sleep, appetite and eating.

6. Most frequent neuropsychological profiles (besides acute stroke)

Subcortical cognitive decline is the most expected profile in patients with diabetes, as for cognitive impairment in other metabolic disorders, and subcortical ischemic vascular disorders related to small vessels disease. It is characterized by forgetfulness, i.e. difficulty in retrieving learned material; slowing of mental and motor processes; impaired ability to manipulate acquired knowledge to generate problem solving; impairment of arousal, attention, and motivation and affective changes (depression), and impairment of set-shifting. Neuropsychological test standard protocols have been proposed for assessing vascular cognitive impairment in 5, 30 or 60 minutes [32].

Typical Alzheimer’s disease is characterized by episodic memory impairment: poor learning over repeated trials, impaired delayed recall, and few benefit from cueing. The memory profile is different from that of frontal-subcortical dementias [33]. Confrontation naming may be early impaired with semantic paraphasias, as well as visuospatial skills.

Frontotemporal dementia is suspected on the basis of history: personality and behavioural changes precede and remain prominent during the course of the disease. Behavioural changes include self-monitoring dyscontrol (behavioural disinhibition, irritability, food taste changes, hyperorality, restlessness…), self neglect (personal hygiene, clothing…), self-centred behaviour (apathy, stereotyped behaviour, social neglect…), affective disorders (mainly flat affect) [34]. At early stages, scores on global scales may be within the normal range, patients are oriented in time and place, and provide correct current autobiographical information (contrary to patients with Alzheimer’s disease). Family members notice a memory impairment but consider it less important than the behavioural disorder and regard it as due to the behavioural changes. Spontaneous speech is usually reduced. Patients have no difficulties in the perceptual recognition of objects and the appropriate use of objects. Executive functions, and must of all social cognition are impaired.
Lewy body dementia is characterized by a subcortical and cortical cognitive profile, with especially severe executive dysfunction and deficits in visuospatial and visuoconstructive abilities. The main features of the disease are fluctuations, visual hallucinations, parkinsonism, and sleep disorders [35]. Lewy bodies and Alzheimer pathology often coexist.

In summary, when patients have a long history of diabetes (especially if they are getting old), have cognitive complaints, unexplained metabolic poor control, or if cognitive and behavioural changes are reported by an informant, it is useful to search for a cognitive decline. The patient may then be referred to a memory clinic for a work-up including brain imaging, to identify the cause of this decline leading to an appropriate medical and medico-social management.

7. Conflict of interest

In the last 3 years, Florence Pasquier has participated in pharmaceutical trials in dementia and cognitive impairment: Bioprojet, Exonhit, Ipsen, Medivation, Wyeth, BMS, Bayer. She served as a member of a scientific committee for a study for Servier and for Ipsen, and as a member of an advisory board for a radiotracer for Bayer.

References